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A STUDY OF THE FRIEDEL AND CRAFTS' REACTION

BY

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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ENTITLED..... A STUDY OF THE FRIEDEL AND CRAFTS' REACTION

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

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This problem was suggested by Dr. Oliver Kamm. The author wishes to thank him for his many suggestions and untiring assistance.



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Introduction.

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The Friedel and Crafts' reaction is a reaction used primarily in the synthesis of aromatic hydrocarbon compounds. The reaction as it is generally carried out is the union of benzene, or, in some cases a benzene derivative, with an alkyl halide in the presence of aluminum chloride. The reaction is very interesting and has been studied extensively but its application and interest seem by no means to have been exhausted. Aluminum chloride is also used in synthesizing various other compounds, amongst which are the ketones, acids and aldehydes.

In some of these reactions it may be pointed out that the yield is increased proportionally ~~to~~, while in others the amount of product does not depend on the proportion of aluminum chloride present. It is interesting theoretically to know just what the action of the aluminum chloride is in these different reactions in which it takes part. Is it a catalyst in all cases? Does it enter into the reaction or does it act differently in different cases? In the present work an attempt is made to throw some light on these reactions by the study of production of phenol and some other products by the passage of pure oxygen into benzene at the boiling point in the presence of aluminum chloride.

A study of the equilibrium produced by the Friedel and Crafts' reaction, is also studied in the hope that some further information may be obtained about this method of synthesis.

That an equilibrium can be and is produced seems to be almost beyond doubt. The fact is easily demonstrated. For instance, the equilibrium may be shown to exist by arriving at it from either side. First, pure mono-ethyl benzene together with benzene in definite quantities may be refluxed for a length of time in the presence of aluminum chloride and the products separated and purified. It will be found that ethyl, di-ethyl and tri-ethyl benzene are present together with some pure benzene. This equilibrium will not be changed by further refluxing of the combined products with aluminum chloride. Now approaching the equilibrium from the other side; quantities of benzene and ethyl bromide in proportions and amounts theoretically to produce the same amount of ethyl benzene and benzene started with before are taken and refluxed with aluminum chloride and the products separated and purified as before. It is found that the proportions of mono-ethyl, di-ethyl, tri-ethyl benzene and benzene in the two cases are the same. By this fact the proof of an equilibrium is established.

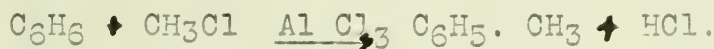
The question involved here is to determine whether the reaction of the aluminum chloride is or is not an equilibrium reaction.

A hydrocarbon is synthesized by the Friedel and Crafts' reaction for general information as to how the reaction goes. A benzene derivative to be obtained from benzene and trimethylene bromide is selected because this halogen compound has not previously been used in the Friedel and Crafts' reaction. This reaction is very interesting on account of its wide application. A study of its theory is also interesting because through a knowledge of the theory the scope of the reaction may be extended or it may be made more effective in its present uses.

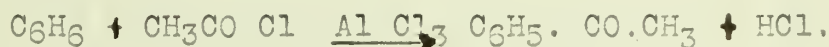
Several theories have been advanced to explain the exact action taking place but none have been accepted without question.

Historical Part.

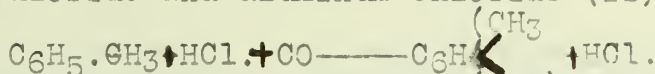
The Friedel and Crafts' reaction, a reaction which has had an extremely wide and varied application in organic chemistry synthesis, was discovered in 1877 by C. Friedel and J. M. Crafts (I) It is connected more particularly with the synthesis of aromatic hydrocarbons, but it is also used in synthesizing a variety of other organic compounds, such as alkyl halides, acid chlorides, ketones, aldehydes and acids. The reaction may also be used to produce internal condensation. Due to the dehydrating action of anhydrous aluminum chloride (V) under some conditions it may also produce decomposition. Finally it may accomplish a transfer of carbons from one carbon atom to another within the benzene nucleus. The active agent in the reaction is aluminum chloride, ferric chloride has also been used but to a lesser extent. Hydrocarbons can be obtained by combining an alkyl halide, e. g. methyl chloride with benzene in presence of aluminum chloride. There is a vigorous evolution of hydrogen chloride with the formation of toluene.



Ketones are prepared in the same way using an aromatic hydrocarbon and an acid chloride.



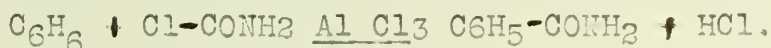
Aldehydes have been obtained by uniting an aromatic hydrocarbon with a mixture of carbon monoxide and hydrogen chloride in the presence of dry cuprous chloride and aluminum chloride (II)



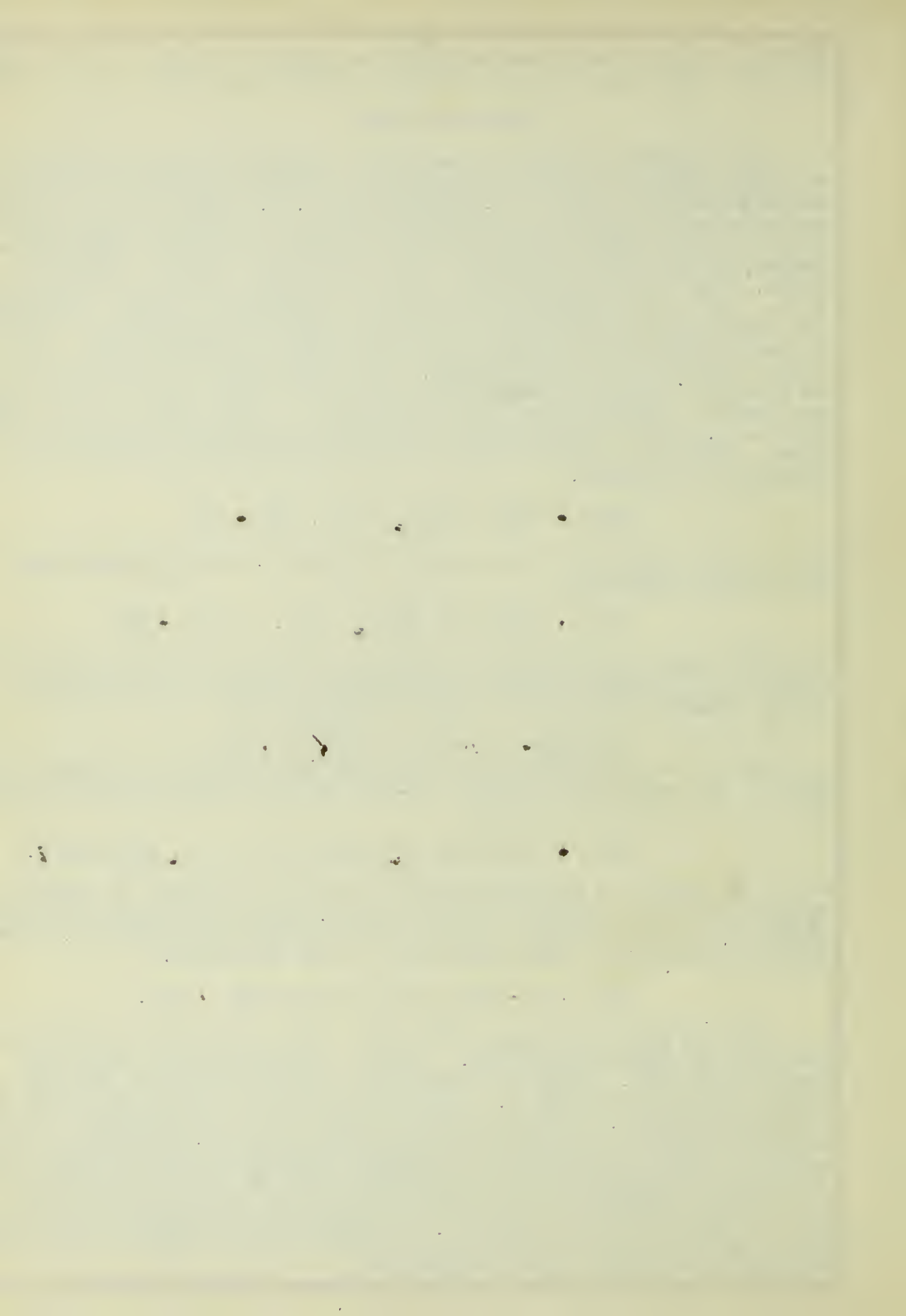
Acids can be prepared by either the (CHO) action of carbonyl chloride in the proportion required theoretically to give the acid chloride, which is then hydrolyzed,



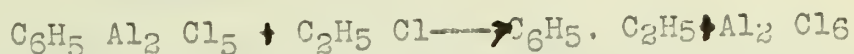
Or by the action of chloroformamide, which is obtained by heating cyanic acid in a current of hydrogen chloride, the vapors being passed directly into the hydrocarbon containing aluminum chloride. The amide of the acid is then hydrolyzed to the free acid.



Kipping and also Combes (III) have done some work on condensation produced by aluminum chloride. Aromatic compounds with long side chains were used. After treatment with aluminum chloride complex ring structures had been formed. An aluminum mercury couple will also produce condensation. Jacobson (6) has shown that if hexamethyl benzene, to which a small amount of aluminum chloride has been added, was heated for a while in a current of hydrogen chloride, methyl groups were successively detached with the formation of lower alkylated products. It is also interesting that methyl groups may be changed from one carbon to another by this reaction. Anschütz and Imundorff (VII) obtained from toluene both benzene and meta and para xylene by refluxing the toluene with aluminum chloride.



Several theories have been advanced to explain the curious changes produced by aluminum chloride and ferric chloride. Friedel and Crafts assumed the formation of an intermediate compound $C_6H_5 Al_2 Cl_5$ which unites with the alkyl halide to regenerate aluminum chloride.



This equation would represent the aluminum as a true catalyst. In practice, however, this is not found to be the case. For in certain reactions it is found that the amount of product increases proportionally with the amount of aluminum chloride present. As Steele has pointed out, this does not necessarily preclude the action of aluminum chloride as a catalyzer, providing it can be shown that it forms a stable compound with the product. The observations of Justavson and others seems to point in this direction. A number of definite compounds have been isolated which seem to act as catalysts, for example $Al_2 Cl_6$, $6C_6H_6$, and with ethyl chloride- $Al_2 Cl_6$, $C_6H_3 (C_2H_5)_3$, $6C_6H_6$.

Steele (XVI) concludes that the action of aluminum chloride and ferric chloride in inducing the Friedel and Crafts' reaction differs from many cases of true catalysts only in the accident that these reagents combine with certain substances produced during the reaction and are thus removed from the system.

This reaction has also had varied use in the preparations of compounds other than hydrocarbons (IX) For example when dry oxygen or air is passed into cold benzene in presence of aluminum chloride, a very small amount of phenol is formed. But when the mixture is heated and run at its boiling point, phenol is produced in much larger quantities. Meta cresol may be obtained from toluene in like manner.

When sulphur and benzene are heated together at $75-80^\circ$ in presence of aluminum chloride until the evolution of hydrogen chloride and hydrogen sulphide ceases and the products separated, phenyl mercaptan, phenyl sulphide, and diphenylene sulphide are found present.

Also benzoic acid, paratoluene^{NE} ortho-benzoic acid, acetophenone^{NE}, aluminum^{NE} phenyl and other compounds may be prepared by the use of aluminum chloride.

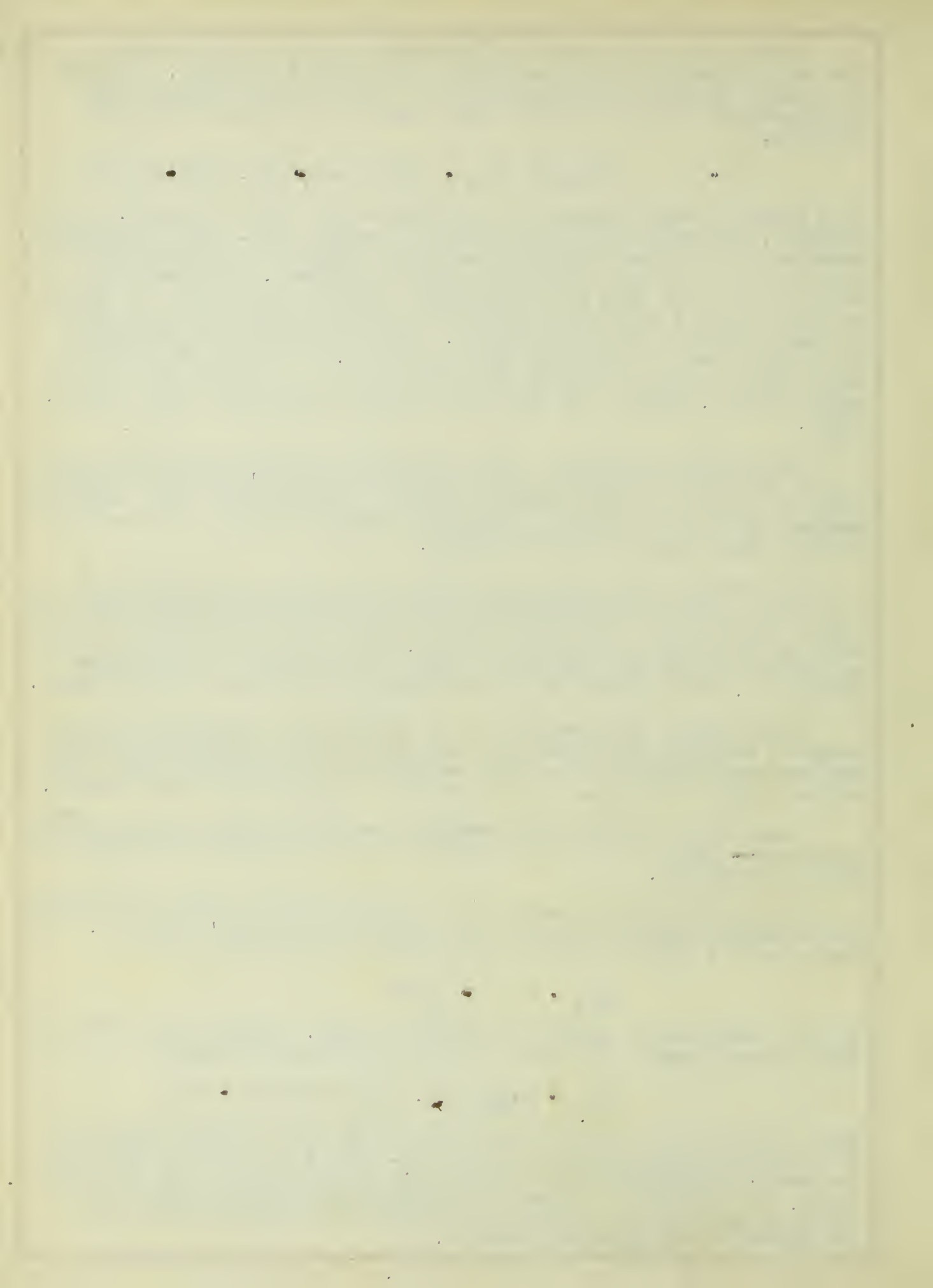
The production of phenol forms the basis for a theory as to how the aluminum chloride provokes the Friedel and Crafts' reaction. The production of phenol might be represented by the reaction.



But the reactions is hardly explained by this. Friedel and Crafts in their second papers (X) wish to explain the reaction thus:



Upon treating this crude product with water the aluminum compound is decomposed and the phenol is liberated. So it is evident here that the aluminum chloride does not induce the reaction by its mere presence. The connection between the hydrocarbon and the chlorine compound is made by one giving up hydrogen, the other chlorine with the formation of hydrogen chloride.

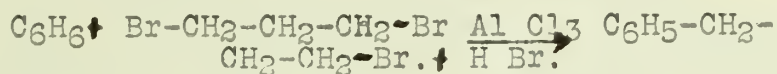


Therefore, it appears that the aluminum chloride does not act as a catalyzer for it is used up in the reaction and must be employed in proportions correspondent to the product to be formed.

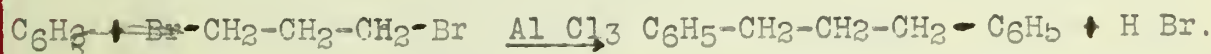
Theoretical Part.

The Friedel and Crafts' reaction has been advanced as a general method of preparing aromatic hydrocarbons with aliphatic side chains. It has also been used in making ketones, acids, aldehydes, and a variety of other compounds. Therefore, the first part of this work will take up the synthesis of one of these compounds, a compound with an aromatic nucleus, but with an aliphatic side chain.

Theoretically the following equation should represent the reaction.

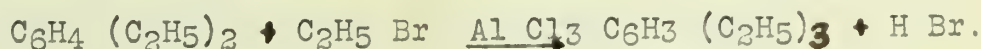
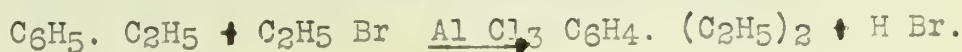
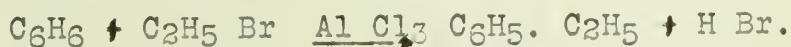


It is more than probable that there is also the side reaction,

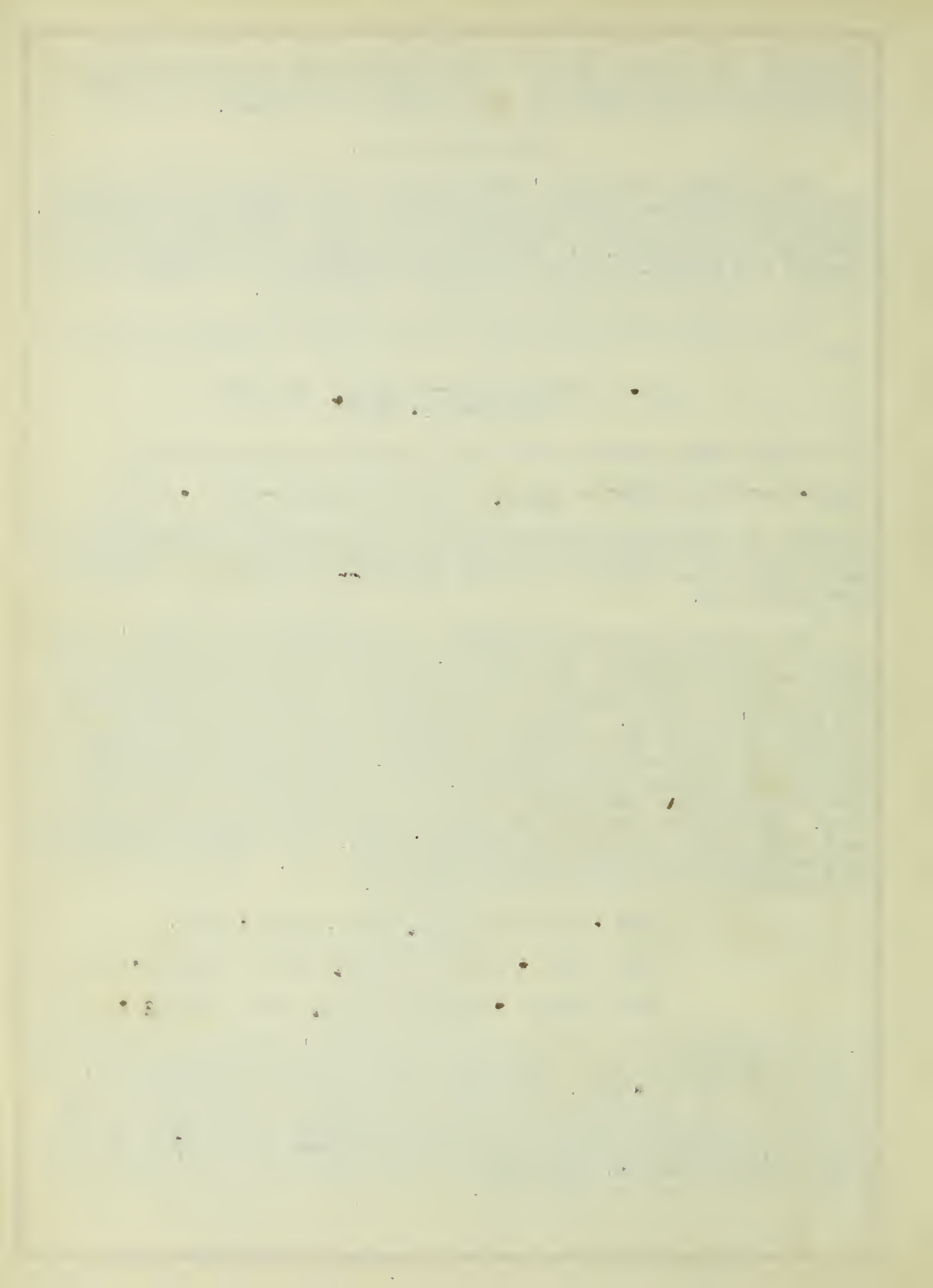


In order to limit the reaction and form the monobrom compound, the reaction must be controlled by using molecular quantities of reagents and stopping the reaction when one molecule of hydrogen bromide has been given off.

An important question involved in the Friedel and Crafts' reaction is the proof of an equilibrium. In this work the study of the ethyl benzene synthesis was chosen because it represents one of the most characteristic examples of equilibrium produced by the Friedel and Crafts' reaction. Benzene and ethyl bromide in the presence of aluminum chloride give monoethyl benzene and along with it smaller proportions of di- and tri-ethyl benzenes. The reaction represents an equilibrium between these products. It has already been mentioned that alkyl groups may either be put in or taken out of the benzene ring. This would also seem to indicate that the reaction in the present case might be of an equilibrium nature. The results obtained in this work have definitely proved this to be true. The reaction may be represented by the following equations.



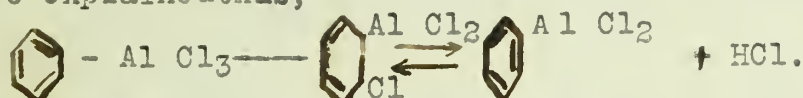
S. D. Kirkpatrick in a thesis for his Bachelor's degree at the University of Illinois in 1916, determined this equilibrium accurately, working on the same reaction. He drew a chart from his results in such a form that it is now possible to take any point in the curve and use the corresponding amounts of reacting substances, treat them in the same way, and get a definite equilibrium between the monodi- and tri-ethyl benzenes formed. The object of the work here is to check one point in the curve on this chart.



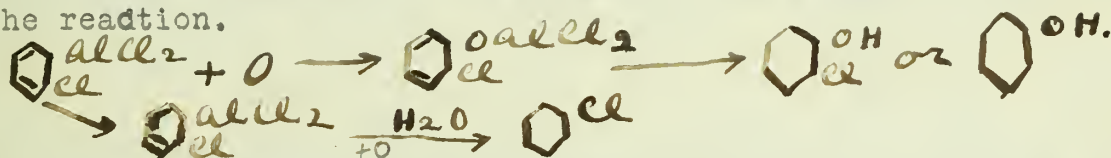
The theories have been advanced to explain how aluminum chloride induces the Friedel and Crafts' reaction. It was first maintained that the action of the aluminum chloride was that of a catalyst (I) and second it is claimed that the aluminum chloride takes part in the reaction and is used up proportionally. (X). Friedel and Crafts' in their first paper (I) attempted to show and explain that the aluminum chloride forms compounds with the benzene which in turn act as catalysts and are decomposed to reform the aluminum chloride or that it forms stable compounds with certain products of the reaction. This theory was modified by certain discoveries disclosed in their second paper. (IX).

They discovered that it was possible to synthesize phenol from benzene and oxygen, phenyl mercaptan from benzene and sulphur in the presence of aluminum chloride, and also acetophanone by treating aceticanhydride and benzene with aluminum chloride.

When we reflux benzene and aluminum chloride together very little hydrogen chloride is given off. It is possible that the reaction may be explained thus,



The aluminum chloride adding to a double bond in the benzene ring to form $\text{C}_6\text{H}_5\text{Al Cl}_2$, this compound then breaking down to give $\text{C}_6\text{H}_6\text{Al Cl}_2 + \text{HCl}$. Further evidence in support of this theory may be cited by the production of phenol by simply passing oxygen or air into this mixture of aluminum chloride and benzene. These equations may represent the reaction.



The fact that some chlorinated products are actually obtained is evidence in favor of the above. In all of these reactions, it was discovered that the yields were proportional to the amount of aluminum chloride used in proportion to the other reagents. For instance the equation.



would hardly explain what takes place in the production of phenol. It is more likely that the reaction takes the following form since hydrogen chloride is given off and the aluminum chloride is its only source.



The aluminum chloride compound is decomposed by adding water and the phenol is liberated.

This reaction may be compared to the Grignard reaction which was not known at the time when Friedel and Crafts carried out their experiments. Here the metal magnesium forms a similar compound. The production of phenol by the Grignard method is represented by the following equation.



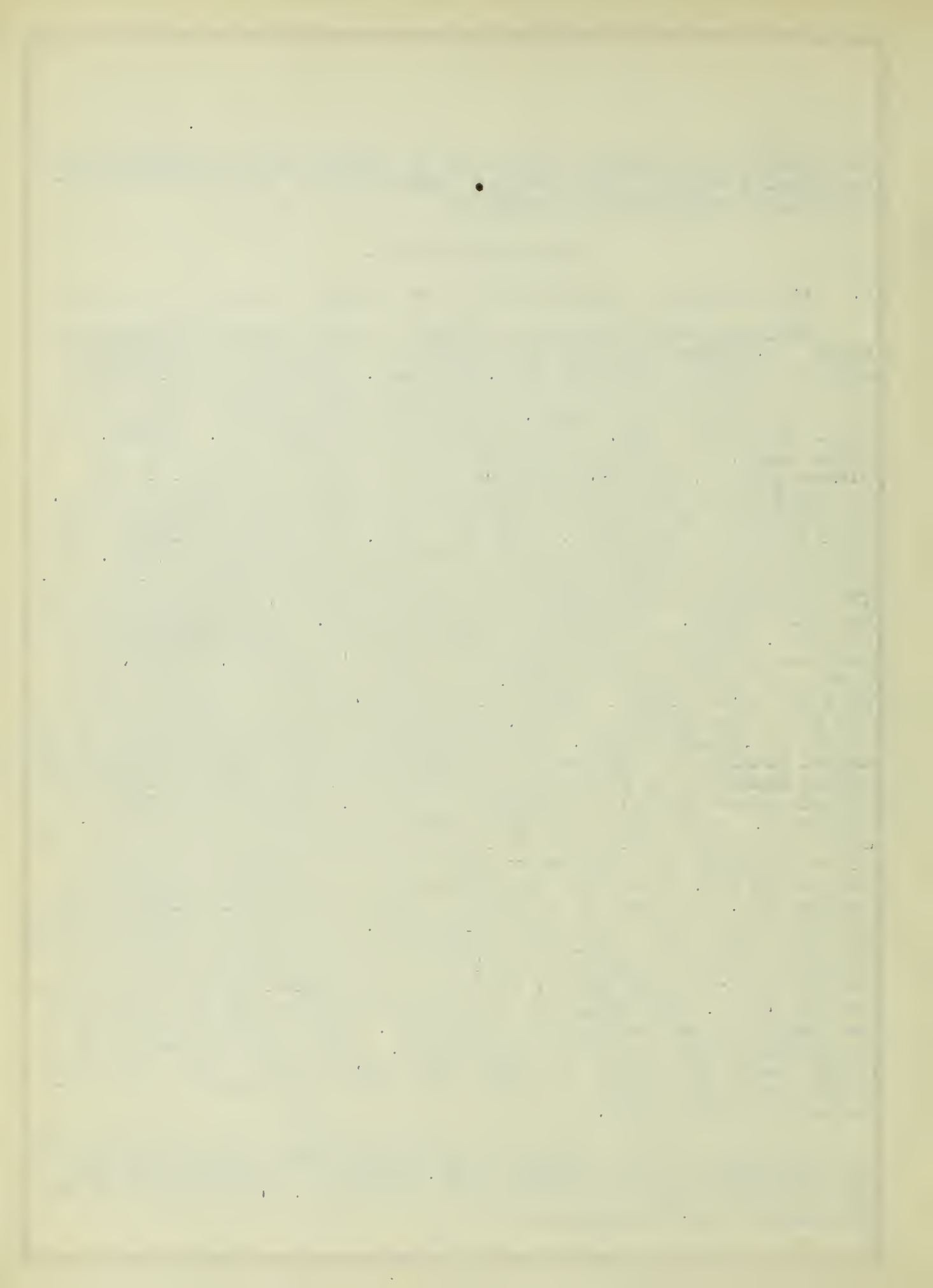
The production of phenol when oxygen is passed into a benzene-aluminum chloride mixture thus presents some evidence in favor of the intermediate organo-metallic compound

Experimental Part.

A. Preparation of a hydrocarbon by the Friedel and Crafts' reaction

Beginning with trimethylene glycol, a very common dihydroxy alcohol, the dibrom compound was prepared by treating with hydrobromic acid of a specific gravity of 1.40 to 1.44. 2 mols of glycol with 5 mols of hydrobromic acid were placed in a large flask to which 2 mols of sulphuric acid were added. The proportions actually used were 152g. of glycol, 850g. of hydrobromic acid, and 110 cc. of conc. sulphuric acid. This mixture was distilled gradually upon which the dibrom propane, $\text{Br-CH}_2\text{-CH}_2\text{-CH}_2\text{-Br}$, passed over with water. It was contaminated slightly with the monobrom compound, $\text{HO-CH}_2\text{-CH}_2\text{-CH}_2\text{-Br}$. The oil layer was separated from the water layer and shaken with an equal volume of cold conc. sulphuric acid. The oil was washed with dilute sodium hydroxide solution after separating from the acid. It was dried over calcium chloride for several hours and then distilled. The boiling point was between 165 and 168 degrees. The yield was about 51 percent. From 760 g. of glycol 1080g. of dibrom propane were obtained. From this purified dibrom propane, dibrom- γ -Phenyl propane was prepared by the Friedel and Crafts' reaction. Practically 2 mols of dibrom propane (400g.) and about 2 mols of benzene (155g) were put into a flask. 75g of aluminum chloride were added gradually. The whole was refluxed using an efficient condenser to prevent the escape of benzene vapors. It was determined when two molecules of hydrogen bromide had been evolved by passing the gas into a solution of sodium hydroxide to neutralize 2 mols of HBr. 160 grams of somewhat impure sodium hydroxide dissolved in 250 cc. of water were used in this work. When the alkali became neutral it indicated that an amount of bromine equivalent to one molecule from each molecule of the dibrom compound had been removed and that the reaction had gone as far as desired. The flask was removed and its contents poured over cracked ice. The ice was allowed to melt and the whole mixture placed into another flask and steam distilled. The desired product is not volatile with steam, therefore the residue in the flask from the steam distillation was extracted with ether, the ether extract dried over calcium chloride for several hours, separated from the calcium chloride and distilled. The ether was distilled off first then the remainder was distilled and collected in fractions. The range of temperature of the distillation was 250 to 360 degrees. What came over ranged in color from a wine color to a very dark reddish brown, the color change being from light to dark with the increase in temperature. Much decomposition took place.

A second attempt was made to synthesize this compound, by varying the proportions of the reagents used. Here the proportion was one mol of dibrom propane with four mols of benzene. Also only 20 grams of aluminum chloride were used.



The process was carried out in the same manner as before except that the final product was distilled under a diminished pressure of 55 to 60 mm. The distillate was a clear, yellow liquid, which was collected in three fractions 120-190, 190-210, and 210,-220 degrees.

Fractions.	Tested with silver nitrate in the cold.	Tested with silver nitrate in hot solution
120-190°	White milky solution.	A brown precipitate
190-210°	A slight cloudiness.	dark precip. formed
210-220°	Very little change.	A slight cloudiness.

It is concluded here, then that in the first attempt very little of the product desired was obtained. This was concluded from the high boiling point of the product, its color, and the fact that there was much evidence of decomposition, and finally, the presence of tarry products as a residue in the distilling flask. In the second attempt it may be supposed that at least a small amount of the phenyl compounds were obtained, both the monophenyl and the diphenyl. The monophenyl being in the second fraction and the diphenyl in the last, in the fraction which did not give the halogen test with silver nitrate. The boiling points of the compounds obtained here compare fairly well with the boiling point of the monophenyl bromopropane prepared by another method and reported in Beilstein's Handbuch as boiling at 110 degrees centegrade at 12 mm. pressure. The boiling point recorded in the literature for 1, 3 diphenyl propane is 298 to 299°. It appears then from the results here that the Friedel and Crafts' reaction is not particularly applicable to this class of compounds where the dihalogen derivatives are involved and where the reaction must be limited to the removal of only one of these halogens.

B. An investigation was made of the equilibrium established between benzene, monoethyl benzene, diethyl benzene and triethyl benzene. S. D. Kirkpatrick in his thesis already referred to in the theoretical and historical parts, obtained his maximum yield of monoethyl benzene and smallest proportions of diethyl and triethyl benzenes by using a proportion of 10 mols of benzene to 4 mols of ethyl bromide. Here the attempt was made to check his results by using the same proportions of reagents. Only half quantities of the above compounds were used. Thipphene free benzene was further purified by redistillation, the fraction passing over between 80 and 81 degrees being taken. The ethyl bromide was purified by treating it with an equal volume of cold conc. sulphuric acid. It was separated from the acid, washed with water, dried over calcium chloride for two hours and redistilled, that fraction being kept which passed over at a temperature within a range of one degree of the boiling point of pure ethyl bromide.

Now in this work, 5 mols of this purified benzene and 2 mols of the ethyl bromide were placed in a flask with 15 grams of aluminum chloride and the whole was refluxed for three hours at the boiling point of the mixture. The hydrogen bromide given off was passed into a solution of sodium hydroxide. At the end of the three hours, the mixture was allowed to cool, shaken with an equal volume of water, the two layers separated and the oil layer dried over calcium chloride. The wash water was distilled for a short time in order to recover small amounts of suspended hydrocarbons.

Before refluxing there was a total of 590 c.c. of the reacting liquids; after refluxing the amount was 450 cc. The loss may be accounted for by some loss in refluxing; and also, it may be true that the volume of the product is less than that of the reagents.

The hydrocarbon mixture was subjected to fractional distillation. The results after two fractionations were as follows:

benzene	264 cc. wt.	233g.	equals	3 mols.
monoethyl "	149 cc. "	130.2g.	"	1.2 "
diethyl "	17 cc. "	15. g.	"	.11 "
triethyl "	3 cc. "	2.6g.	"	.015 "

There were then actually 4.5 mols of benzene and 1.45 mols of ethyl bromide engaged in the reaction. This yielded 133 grams of monoethyl benzene, 20 grams of diethyl benzene, and 2 grams of triethyl benzene. These results were changed to the basis of 10 mols of benzene by multiplying all results by 2.22. Putting these results into tabular form they may be compared with the results obtained by S. D. Kirkpatrick.

Results obtained in this work.
for 3.1 mols of ethyl bromide
reacting with ten mols of benzene.

Monoethyl benzene.	292.6g.
diethyl "	44.3g.
triethyl "	4.4g.

Results obtained by S. D. K.
for 3.1 mols of ethyl bromide
reacting with 10 mols of benzene.

310g.
40g.
4g.

All of the above fractions resulting from the fractionation of the benzene and ethyl benzene mixtures were recombined and refluxed again for three hours with 15 grams of aluminum chloride, treated as before, and again fractionated. The resulting products were very slightly changed in amounts. This fact only goes farther to prove that an equilibrium is established between these compounds, since the proportions are not changed on further treatment with aluminum chloride. The results here, then practically check with those obtained in the other thesis. What variation there is in the results may be due to differences in experimental conditions and to care in operation. Therefore, it may be said that this work is a practical check on the other and verifies the results previously obtained.

C. An Attempt to determine the mechanism of the Friedel and Crafts' reaction.

The theories which have been advanced are discussed in the theoretical part of this thesis. The experimental part here deals with the production of phenyl by passing oxygen into benzene in the presence of aluminum chloride. Thiophene-free benzene was further purified by distillation, collecting the fraction passing over between 80 and 81 degrees. 300 cc. of this purified benzene together with 25 grams of aluminum chloride were placed in a flask fitted with a reflux condenser. A stream of oxygen, purified by passing it through a strong alkali solution and then through conc. sulphuric acid, was passed to the bottom of the flask at such a rate that the gas would bubble up slowly through the benzene. The flask was heated gently until its contents reached the boiling point, which temperature was maintained throughout the reaction. After fifteen liters of oxygen had been passed through the solution, the contents of the flask became dark brown in color.

The time required was about three hours. After cooling, the contents of the flask were poured into water and shaken well. The layers formed were separated and the oil was dried over calcium chloride for several hours. The product was distilled and collected in fractions. 240 cc. passed over between 80 and 88 degrees, leaving a residue of 5 cc. It is assumed that there were chlorinated benzene products here which raised the boiling point of the benzene. Although chlorobenzene boils at 132 degrees, a small quantity might easily escape detection when in the presence of large amounts of benzene. The first fraction, however, was not refractionated so it is not certain that chlorobenzene was present. The 5 cc. fraction was placed in a small distilling bulb and distilled. It began passing over at 180 degrees, about the boiling point of phenol, and this boiling point rose steadily until it reached 350 degrees where the distillation was stopped. In the distillate, the odor of phenol was very pronounced. It is safe to conclude here then that phenol was formed, but the amount was very small and it would have been difficult to separate it out as a pure compound. That it was present, however, was confirmed by the fact that water in which some of this oil was shaken gave a positive phenol test with bromine water. This test, however, was not confirmed by the ferric chloride color test, which may have been due to the presence of a trace of acid as an impurity. The higher boiling fractions of this residue are evidently mixtures of phenol derivatives, possibly chlorophenols or cresols or both. It is possible that the aluminum chloride performs a double function here, decomposing some of the benzene to form toluene and the xylenes, which in turn in the presence of oxygen react to form cresols and other higher boiling compounds. This is entirely in accordance with the experimental results obtained by Friedel and Crafts and reported in the first paper (I). These investigators synthesized toluene and the xylenes simply by refluxing benzene with aluminum chloride.

In this experiment since phenol is formed and hydrogen chloride given off, it can hardly be assumed that the reaction is so simple as to be expressed by the equation.



The evidence points to the conclusion that the following equation represents the reaction. $\text{C}_6\text{H}_6 + \text{O} \longrightarrow \text{Al}_2\text{Cl}_6 \longrightarrow \text{C}_6\text{H}_5\text{O Al}_2\text{Cl}_5 + \text{HCl}$. Here the aluminum compound remains in solution until decomposed by water, by which the phenol is set at liberty.(X).

It was hoped to identify chlorobenzene as one of the products of the reaction. Its presence would yield some experimental evidence in proof of the formation of the additional product $\text{C}_6\text{H}_4\text{AlCl}_2\text{O}$, as an intermediate in the Friedel and Crafts' reaction. The amount of chlorobenzene is, however, so small that no separation from the excess of benzene was possible.

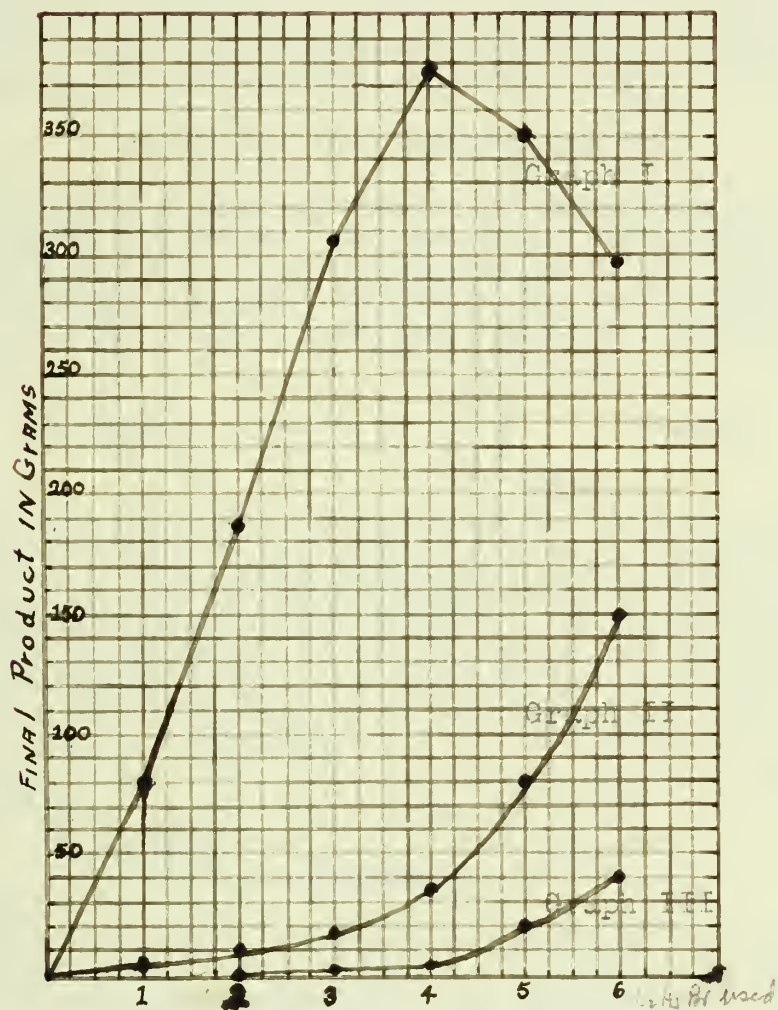
Summary to Part I

The results of this study of the Friedel and Crafts' reaction may be summarized briefly. It was found first, that the Friedel and Crafts' reaction is not particularly applicable in syntheses involving tri^methylene bromide in which the reaction must be limited to one of two halogen atoms.

Second the Friedel and Crafts' reaction was found to be an equilibrium reaction, the equilibrium between the products being changed only when the amounts of the reacting substances are changed.

And finally, from this work it may be concluded that aluminum chloride acts in at least two different ways in inducing the Friedel and Crafts' reaction. In one type of experiment it may be classed as a catalyzer, while in another it is evidently one of the reactive compounds and is used up in the reaction. For example, in the synthesis of ethyl benzene the yield does not depend upon the amount of aluminum chloride present but the reaction is independent of the amount of aluminum chloride provided there is enough present to act as a catalyzer. But again, in the production of phenol by passing oxygen into benzene and aluminum chloride the yield of phenol is proportional to the amount of aluminum chloride present. Here the action cannot be considered as catalytic, for it has been demonstrated in this work that the aluminum chloride is used up in the reaction.

Reproduction of S. D. Kirkpatrick's Graph of the production of Mono-ethyl, di-ethyl and tri-ethyl benzene is on the following page.

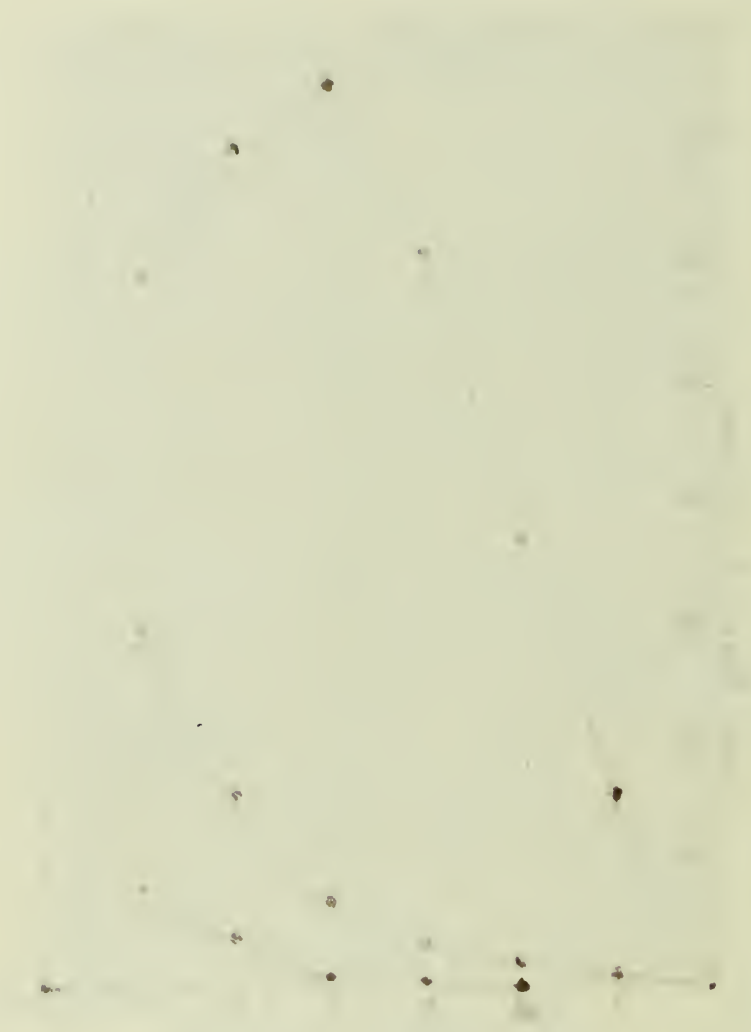


ETHYL BENZENE SYNTHESIS
By
FRIEDEL AND CRAFTS' REACTION

Graph I. Yield of Mono-ethyl Benzene.

Graph II. Yield of Di-ethyl Benzene.

Graph III. Yield of Tri-ethyl Benzene.



The Preparation of N-ethyl-p-aminophenetol.

Introduction

The second part of this thesis is concerned with some general organic syntheses. It is an attempt to synthesize and to study the synthesis of n-ethyl-para-aminophenetol, which has not as yet been described in the literature. Incidentally it was hoped to obtain a new and technically better method for the synthesis of p.-nitrophenol. P-nitraniline, the basis for this compound, may be obtained in the open market for not more than one dollar per pound. Also, there is much opportunity to improve the preparation methods for the other individual intermediate compounds. For instance, the method used here may prove to be a much more convenient and better method of synthesizing para-aminophenetol than any commonly in use at present.

Historical and Theoretical Part.

The method used for the synthesis of the sodium salt of p-nitrophenol was suggested by Lange: "Die Schwefel Farbstoffe". It is claimed that the method is used commercially for the preparation of the sodium salt of nitrophenol, but this statement could not be verified in the literature. The following equation represents the reaction.



Para-nitrophenetol was prepared from the sodium salt of p-nitrophenol. According to Beilstein (XIII) p-nitrophenetol has been prepared by heating the 2-nitrotoluolsulphonic acid ester of p-nitrophenol with alcoholic potash for 36 hours. Here this compound is prepared by heating the sodium salt of p-nitrophenol with ethyl bromide, the ethyl bromide being present in slight excess of the required amount in order to drive the reaction to completion. The reaction which takes place is as follows:



Para-aminophenetol was prepared by reducing the para-nitrophenetol with powdered iron. The method is analogous to that used in the preparation of aniline commercially from nitrobenzene. (XI). It will be noticed in the experimental part that only a very small amount of hydrochloric acid is used to produce a reaction which theoretically should require much more. Why does the iron continue to reduce the nitro groups when the acid required in the action is theoretically used up? Roscoe and Schorlemmer (VIII) claimed that the initial reaction is followed by the reduction of nitrobenzene by means of ferrous chloride and hydrochloric acid.

$\text{C}_6\text{H}_5\text{NO}_2 + 6\text{HCl} + 6\text{FeCl}_2 \longrightarrow \text{C}_6\text{H}_5\text{NH}_2 + 3\text{FeCl}_3 + 3\text{H}_2\text{O}$, but reduction in this way cannot be realized experimentally.

A more satisfactory explanation has been made by Muspratt (XVIII). He says that aniline ~~and~~ the ferric chloride in the first steps of the reaction interact to give ferrous hydroxide and aniline hydrochloride, the latter then reacting with metallic iron to liberate hydrogen or effect reduction. $2 \text{C}_6\text{H}_5 \cdot \text{NH}_2 + \text{Fe Cl}_2 + 2 \text{H}_2\text{O} \longrightarrow 2 \text{C}_6\text{H}_5 \text{NH}_2; \text{HCl} + \text{Fe} (\text{OH})_2 + 2 \text{C}_6\text{H}_5 \text{NH}_2; \text{HCl} + \text{Fe} \longrightarrow 2 \text{C}_6\text{H}_5 \text{NH}_2 + \text{Fe Cl}_2 + \text{H}_2$. Both of these reactions can be confirmed experimentally.

A more fundamental explanation of the process, however, is put forward by Raikow. He attributes the continuation of the reduction primarily to hydrolytic dissociation of the ferrous chloride. The hydrochloric acid so formed, then reacts with metallic iron to liberate hydrogen or to effect the reduction of nitrobenzene. $\text{C}_6\text{H}_5 \text{NO}_2 + 3 \text{Fe} + 6 \text{HCl} \longrightarrow \text{C}_6\text{H}_5 \text{NH}_2 + 3 \text{Fe Cl}_2 + 2 \text{H}_2\text{O}$; $3 \text{Fe Cl}_2 + 6 \text{H}_2\text{O} \longrightarrow 3 \text{Fe} (\text{OH})_2 + 6 \text{HCl}$. $3 \text{Fe} (\text{OH})_2 + 6 \text{HCl} + 3 \text{Fe} + \text{C}_6\text{H}_5 \text{NO}_2 \longrightarrow 3 \text{Fe} (\text{OH})_2 + 3 \text{Fe Cl}_2 + 2 \text{H}_2\text{O} + \text{C}_6\text{H}_5 \text{NH}_2$. The reduction of the para-nitrophenetol is accomplished here then by analogy to the reduction of nitrobenzene to aniline.



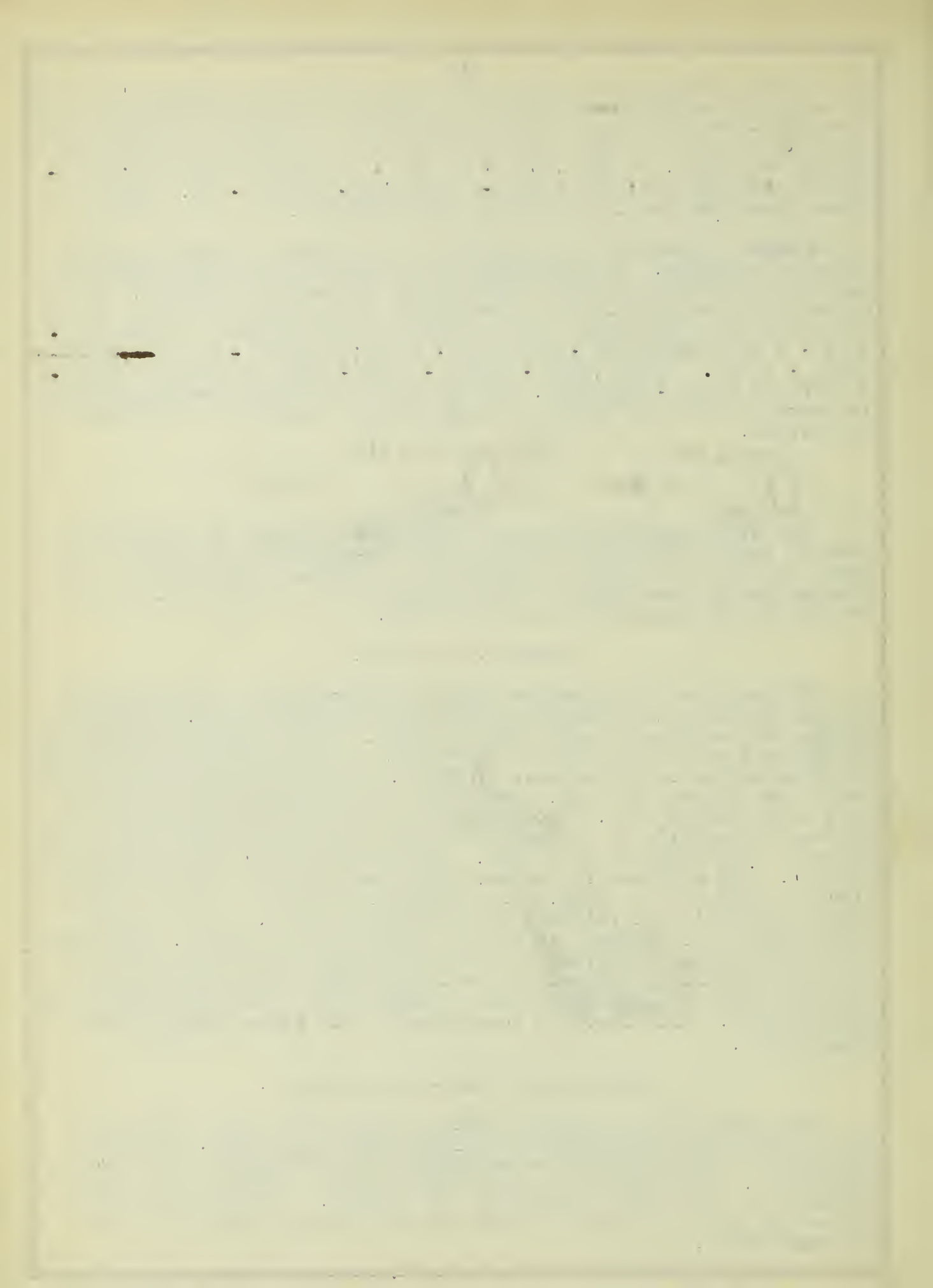
The ethyl-aminophenetol was prepared by analogy to the method used by Noyes (XIX) in preparation of mono-ethyl aniline; that is, using the amino compound and treating it with an alkyl halide. The same method is also used in the preparation of the ortho-mono-ethyl aminophenetol reported in Beilstein (XV).

Experimental Part.

Preparation of the sodium salt of p-nitrophenol. 100 grams of para-nitraniline were treated with a solution of 75 grams of sodium hydroxide dissolved in one liter of water. The whole was refluxed at the boiling point until all of the nitraniline was dissolved and the solution became clear and dark in color. It was then removed from the reflux and allowed to cool, upon which the product crystallized out as a heavy yellow mass. The precipitate was filtered off and to the filtrate a quantity of concentrated alkali equal to one-fourth of the volume of the filtrate was added. More of the sodium salt crystallized out. The sodium salt was recrystallized from hot water by dissolving the salt in hot water, filtering while hot, then adding concentrated alkali to the filtrate and allowing to cool. The salt was then dried at 110 degrees in the hot air oven and weighed. The yield is between 80 and 85 percent of the theoretical yield and the color of the crystallized product varies from a yellow to a deep orange, depending upon the concentration of alkali from which the salt was recrystallized. This reaction runs smoothly and gives comparatively good yields.

Synthesis of para-nitrophenetol.

200 grams of the carefully dried sodium salt of p.-nitrophenol were heated with one liter of absolute alcohol and 140g. of ethyl bromide in an autoclave ~~in an autoclave~~ for four hours at 100 degrees centigrade. The pressure on the inside of the autoclave was about 5 atmospheres when this temperature was reached. At the end of about three and one half hours the pressure rose fairly rapidly to almost 15 atmospheres.



At the end of the period, the mixture was removed from the autoclave, the alcohol distilled off, water added and the whole steam distilled. The product passed over as an oil. This oil steam distilled very slowly since it required about 10 hours to remove it from the residue in the flask. The water layer and the oil layer were separated, the oil layer redissolved in hot alcohol and recrystallized. Much care must be exercised in this recrystallization in that the alcohol must be cooled suddenly, or the product will precipitate out as a very crude looking compound. 50 grams of a very good crystallized product were obtained here, or a yield of 28 percent of the theoretical, which is slightly less than 200 grams. From the alcohol used in this reaction 155 cc. of pure ethyl ether were obtained upon redistillation. The ether explains the loss of the ethyl bromide and accounts for the low yield.

A second experiment similar to the one above was run. It was the same in every detail except that instead of using the autoclave and synthesizing the compound under increased pressure, the mixture was refluxed at atmospheric pressure using an efficient condenser in order to prevent the escape of the very volatile ethyl bromide. Here the refluxing was continued for 25 hours, the yield was 70 percent of the theoretical yield with no ethyl ether formed as was the case when the same compound was made in the autoclave. A melting point determination showed the product to melt at 60 degrees.

The reduction of nitrophenetol to aminophenetol.

60 grams of nitrophenetol were slowly added to a beaker which contained 120 grams of powdered iron, 3 cc. of conc. hydrochloric acid and 90 cc. of water. The contents of the beaker were stirred constantly while the addition of the nitrophenetol was continued and the beaker was kept at the temperature of the steam bath. It was necessary to add small quantities of water, from time to time, to the contents of the beaker in order to prevent solidification. After all the nitrophenetol had been added the beaker was heated on the steam bath until the odor of nitrophenetol had completely disappeared. From 60g of nitrophenetol used, 17.5g. were recovered unchanged. The aminophenetol was separated by extracting the contents of the beaker with ether. This ether solution was dried over anhydrous sodium sulphate, then the ether distilled off and the residue distilled. The boiling point was 244 to 245 degrees. The yield was based upon the 42.5g. of nitrophenetol which were actually changed by the iron and amounted to a 30 percent yield. The color of the product, immediately after distillation, was about that of pure cotton-seed oil, but it turned to a dark color upon standing even though it was kept in a tightly stoppered bottle.

This synthesis was repeated, employing more time in adding the nitrophenetol to the powdered iron reducing agent and the mixture was also heated longer on the steam bath with intermittent stirring, after all of the nitrophenetol had been added. The yield here increased to 60 percent of the theoretical.

Synthesis of N-ethyl-p-aminophenetol.

100 grams of para-aminophenetol were heated for 4 to 5 hours with 84 grams of ethyl bromide at 60 degrees.

The resulting compound was treated with enough sodium hydroxide solution to neutralize any acid present. The product was then removed by extraction with ethyl ether. Several attempts were made to obtain the product in a pure condition.

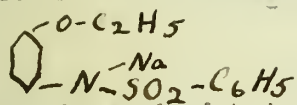
The first attempt was to make the acetyl derivative. It was prepared by taking one cc. of the amine and adding to it two cc. of acetic anhydride. This mixture was heated to boiling, allowed to stand for a few minutes and then poured into ten cc. of water and heated to the boiling point. This procedure decomposed the excess of acetic anhydride. The solution was cooled, the crystals which were formed were filtered off, dried on a clay plate and the melting point taken. It was 148 degrees. The melting point reported in Richter's Lexikon for phenacetin is 150-1 degrees.

The second method of purification was by making the sulphanil derivative. 1 cc. of the crude amine was shaken and warmed with 20cc. of dilute sodium hydroxide. Enough alkali was added in addition to keep the reaction slightly alkaline. The mixture was cooled and a little water added to keep the inorganic salts in solution.

The method used for the separation of the products of reaction was as follows:

Extract the alkaline solution with ether

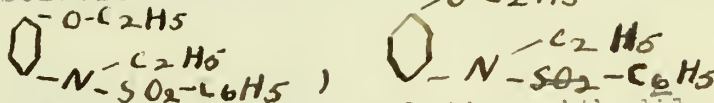
Soluble in alkali.



Acidify and obtain the free sulfonyl derivative.

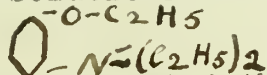
m. pt. 149°

Soluble in ether

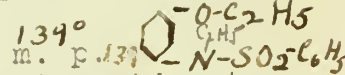


Extract the ether solution with dil. HCl

Soluble in dil HCl.



Soluble in ether



The above examination indicated that the alkylation did not run smoothly, since a considerable quantity of phenetidine was isolated as the sulfonyl derivative. Distillation of the mixture of the free amines showed that mono-ethyl and diethyl phenetidines cannot be effectively separated, even under diminished pressure, unless large amounts of material are available.

Summary to Part II.

(1) p-Nitrophenol was prepared technically by hydrolysis of p-nitraniline. This method, which is not described in the literature was found to be very efficient.

(2) The alkylation of p-nitrophenol was studied both under atmospheric pressure and in the autoclave. Increased pressure was found to favor the production of ethyl ether as a by-product.

(3) The iron reduction method was applied to the reduction of p-nitrophenetol.

(4) p-Aminophenetol was alkylated by means of ethyl bromide.

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